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    Francis-Lang, Helen; Friedman, Lori; Kidd, Thomas; Roche,
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     The invention has designed a dominant loss of function screen to
identify
     genes that interact with the cyclin dependent kinase inhibitor
p21 in
     Drosophila. Casein kinase I gamma-1 isoform 3 (CSNK1G1) gene was
     identified as a modifier of the p21 pathway. Accordingly,
     orthologs of these modifiers, and preferably the human
orthologs, casein
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     the treatment of pathologies associated with a defective p21
signaling
     pathway, such as cancer. The invention also provides methods for
     utilizing these p21 modifier genes and polypeptides to identify
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therapeutic agents that can be used in the treatment of disorders associated

with defective p21 function.

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AN
     1999268046 EMBASE
     Angiotensin II stimulates serine phosphorylation of the adaptor
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protein
     Nck: Physical association with the serine/threonine kinases Pakl
and
     casein kinase I.
     Voisin L.; Larose L.; Meloche S.
AU
     S. Meloche, Centre de Recherche, Centre hospitalier Univ. de
CS
Montreal,
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Campus Hotel-Dieu, 3850 St. Urbain, Montreal, Que. H2W 1T8,

meloches@ere.umontreal.ca

Canada.

SO Biochemical Journal, (1 Jul 1999) Vol. 341, No. 1, pp. 217-223. .

Refs: 44

ISSN: 0264-6021 CODEN: BIJOAK

CY United Kingdom

DT Journal; Article

FS 029 Clinical Biochemistry

LA English

SL English

ED Entered STN: 12 Aug 1999

Last Updated on STN: 12 Aug 1999

AB Nck is a small adaptor protein consisting exclusively of three SH3 domains

and one SH2 domain. Nck is thought to have an important role in cell

signalling by coupling receptor tyrosine kinases, via its SH2 domain, to

downstream SH3-binding effectors. We report here that angiotensin II,

working through the AT1 receptor subtype, stimulates the phosphorylation

of Nck in rat aortic smooth muscle cells. Phosphopeptide mapping analysis

revealed that Nck is phosphorylated on four peptides containing exclusively phosphoserine in quiescent cells. Treatment with angiotensin

II resulted in increased phosphorylation of these four peptides, without

the appearance of new phosphopeptides. We show that Nck, via its SH3

domains, specifically binds three major phosphoproteins of 95, 82 and 66

kDa both in vitro and in intact cells. Notably, the phosphorylation of

these Nck-binding proteins was found to increase in parallel with that of

Nck on stimulation by angiotensin II. One candidate for the $66\,$ kDa

phosphoprotein is the serine/threonine kinase p21-activated
 kinase 1 (Pak1), which was found to form a stable complex with
Nck in

aortic smooth muscle cells. We have also identified the $\gamma 2$ isoform

of casein kinase I as another protein kinase that associates with Nck in

these cells. These findings indicate that Nck is a target of G-protein-coupled receptors and suggest a role for Pakl and casein

kinase I-.gamma.2 in downstream signalling or regulation of the AT1 receptor.

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